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Original Article

Significance of Microcalcifications on Mammography in the Surgical Treatment of Breast Cancer Patients with a Preoperative Diagnosis of Ductal Carcinoma *in Situ* by Core Needle Biopsy

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To clarify the surgical outcomes of breast cancer patients with a preoperative diagnosis of ductal carcinoma *in situ* (DCIS) by core needle biopsy (CNB) (abbreviated as CNBDCIS), we retrospectively analyzed the cases of 131 patients with CNBDCIS who underwent surgery at Oomoto Hospital (32 total mastectomies, 99 conservative mastectomies). Our analysis of underestimation and predictors of invasive breast cancer of CNBDCIS revealed that the underestimation rate of CNBDCIS was 40.5% (53/131). A logistic regression analysis revealed that palpable tumors (yes to no, odds ratio [OR] 3.25), mammography (MMG) category group (category 4 or 5 to categories 1, 2, or 3, OR 4.69) and MMG microcalcifications (no to yes, OR 0.24) were significant predictive factors for CNBDCIS invasion. In our analysis of the predictors of positive margins during CNBDCIS surgery, 36 (27.5%) of the 131 patients had positive margins after postoperative pathological examination. A logistic regression analysis revealed that the operative procedure (conservative surgery to total mastectomy, OR 21.4) and MMG microcalcifications (yes to no, OR 3.35) were significant factors related to positive margins during CNBDCIS surgery. Thus, MMG microcalcifications are a negative predictor of upgrading of CNBDCIS and a positive predictor of positive surgical margins for CNBDCIS.

Key words: ductal carcinoma *in situ*, core needle biopsy, underestimation, positive margins, microcalcifications on mammography

Ductal carcinoma *in situ* (DCIS) of the breast is defined as malignant cells localized in ducts without evidence of invasion through the basement membrane. Since the development of a screening system, the incidence of DCIS has increased [1, 2], and the development of percutaneous core needle biopsy (CNB) technology has increased the number of individuals preoperatively diagnosed with DCIS (abbreviated as CNBDCIS) without incisional biopsy. Surgery is fundamental to the successful treatment of patients with CNBDCIS [3], but there are two main challenges concerning the surgical treatment of CNBDCIS. The first is the possibility of coexisting invasive ductal cancer (IDC), which can lead to the underestimation of DCIS by CNB, and the second is obtaining a safe surgical margin, especially in conservative breast surgery.

A number of reports, including a meta-analysis, have described the clinical and pathological factors contributing to the underestimation of CNBDCIS [3-10]. There are also numerous reports on the difficulties of obtaining positive margins [11-18]. Surgeons should have a good understanding of these problems in order to provide the optimal treatment of patients with CNBDCIS.

Microcalcifications observed on mammography

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(MMG) are commonly detected in patients with DCIS or IDC, but the relationships between MMG microcalcifications and the underestimation of DCIS or positive surgical margins in CNBDCIS have not been sufficiently examined. In the present study, we evaluated the significance of microcalcifications on MMG in relation to the above two problems.

Patients and Methods

Of the 3,020 patients who underwent a CNB at Oomoto Hospital (No. 0111442) between January 2008 and June 2018, the 131 patients with a preoperative diagnosis of CNBDCIS who underwent surgery at the same hospital were enrolled in this study. Secondary breast cancer patients who had undergone a prior partial mastectomy of the ipsilateral breast were excluded. The indication for a CNB at our hospital is suspicion of malignant tumor by mammography or ultrasound (including only calcification on mammography if malignancy is suspected).

Mammography was performed in mediolateral oblique (MLO) and craniocaudal (CC) views using the mammography machines MGU-100B Mammorex (Toshiba, Tokyo). After April 2013, mammography was performed using a Peruru MGU1000D digital mammography system (Toshiba).

The mammography findings were analyzed according to the Mammography Guidelines (3rd edition) issued by the Japan Radiological Society [19]. In the present study, we defined microcalcifications on MMG as positive based on their distribution (segmental, linear, and grouped or clustered) and shape (small round calcifications, fine, branching calcifications, or casting calcifications). The microcalcifications ranged in size from 0.5 mm to 3 mm and were produced in the tumor. Obvious calcifications caused by benign lesions were excluded.

Ultrasound (US) was performed using a US Xario SSA-660A 8 MHz or Aplio XG SSA-790A 12 MHz (Toshiba). The findings were analyzed according to the Guidelines for Breast Ultrasound-Management and Diagnosis (3rd edition) issued by the Japan Association of Breast and Thyroid Sonology [20]. All of the mammography findings and US findings were evaluated by surgeons, including laboratory technicians for US examinations, who were qualified by The Japan Central Organization on the Quality Assurance of Breast Cancer Screening. The preoperative tumor size was measured by MMG or US, whichever depicted the tumor size more clearly.

The US-guided CNB was performed on all patients by surgeons. In 122 patients, a 14-gauge core tissue biopsy needle (Bard Magnum; Bard, Crawley, UK) was used, and in the other 9 patients, a 10-gauge vacuum-assisted biopsy system (Vacora; Bard) was used. The average number of cores was 2.9 (2-6).

Regarding the positive margins, pathological examinations were carried out using paraffin sections and hematoxylin-eosin staining. After formalin fixation for 1-2 days, all specimens were cut perpendicularly at 5-mm intervals for the 99 conservative surgeries and 9 of the 32 total mastectomies. For the remaining 22 total mastectomy specimens, 3-5 cuts were made for the pathological examination of the tumor and margins. The definitive (postoperative) size of the tumor was measured pathologically. The margins were considered positive when cancer cells were detected within 2 mm of the lateral edges or skin side of the specimen except for the bottom side (chest wall side).

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [21]. More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics. In general, p-values < 0.05 by Fisher's exact test, logistic regression, or the unpaired t-test were considered significant. This study was approved by the ethics committee of Oomoto Hospital in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

Results

All 131 patients were females, with an average age of 59.5 years old (35-90 years). Total mastectomy was performed for 32 patients, and conservative mastectomy was performed for 99 patients (87 partial mastectomies, 5 skin-sparing mastectomies, and 7 nipple-sparing mastectomies).

In all 25 patients with only microcalcifications on MMG who underwent a partial mastectomy, mammography of the specimen was done to verify the complete resection of the lesion with microcalcifications.

Ninety-five patients underwent a sentinel node biopsy (SLNB), and 30 patients underwent an axillary node dissection (ALND). Among the 30 patients with ALND (20 total mastectomies and 10 conservative surgeries), 2 had preoperative axillary lymph node swelling, and 1 patient underwent an ALND due to positive sentinel node metastasis on a frozen section. Seven patients had lymph node metastasis. One of the 14 patients with ductal carcinoma in situ with minimal invasion (DCISM) and 6 of the 29 patients with invasive ductal carcinoma (IDC) had lymph node metastases. As a result, the rate of lymph node metastasis was 5.3% among the 131 CNBDCIS patients.

Analysis of underestimation and predictors of invasive breast cancer in CNBDCIS. The results of the univariate analysis (Fisher's exact test) of the clinicopathological factors for CNBDCIS in relation to invasion are presented in Table 1. MMG findings are presented based on the categories described by Wiratkapun *et al.* [8]. Among the 45 patients with only microcalcifications on mammography, the MMG category was 3 in 17 patients, category 4 in 9 patients, and category 5 in 19 patients.

The rate of underestimation of CNBDCIS was 40.5% (53/131). The five factors that were significantly related to invasion by CNBDCIS were as follows: palpable tumor, MMG category group 4-5, MMG microcalcifications, MMG mass, and US category 4-5. Patient age,

Table 1 Clinicopathological factors of the patients with a preoperative diagnosis of DCIS by CNB related to tumor invasion

Factor	Group	Tumor invasion		*p*-value
		DCIS	DCISM (15)+IDC (38)	
n		78	53	
Sex	Female	78 (100.0)	53 (100.0)	NA
Age	＜60	44 (57.1)	21 (39.6)	0.074
	≧60	33 (42.9)	32 (60.4)	
Site	Left	42 (53.8)	21 (39.6)	0.154
	Right	36 (46.2)	32 (60.4)	
Palpable tumor (%)	No	43 (55.8)	10 (18.9)	＜0.001
	Yes	34 (44.2)	43 (81.1)	
MMG findings (%)	Microcalcifications	36 (46.2)	9 (17.0)	
	Mass	21 (26.9)	28 (52.8)	
	Mass with microcalcifications	10 (12.8)	7 (13.2)	
	Asymmetrical density	5 (6.4)	1 (1.9)	
	Architectural distortion	1 (1.3)	5 (9.4)	
	Invisible on mammogram	5 (6.4)	3 (5.7)	
MMG category group (%)	1, 2, 3	43 (55.1)	15 (28.3)	0.004
	4, 5	35 (44.9)	38 (71.7)	
MMG microcalcifications (%)	No	32 (41.0)	37 (69.8)	0.001
	Yes	46 (59.0)	16 (30.2)	
MMG mass (%)	No	47 (60.3)	18 (34.0)	0.004
	Yes	31 (39.7)	35 (66.0)	
US category (%)	2, 3	30 (38.5)	8 (15.1)	0.006
	4, 5	48 (61.5)	45 (84.9)	
CNB nuclear grade (%)	Low	36 (46.2)	34 (65.4)	0.087
	Intermediate	30 (38.5)	14 (26.9)	
	High	12 (15.4)	4 (7.7)	
Comedo necrosis	No	55 (70.5)	45 (84.9)	0.063
	Yes	23 (29.5)	8 (15.1)	
ERPgR (%)	Negative	25 (32.1)	11 (20.8)	0.169
	Positive	53 (67.9)	42 (79.2)	
Preoperative size	Mean (sd) cm	2.63 (1.68)	2.68 (1.75)	0.856

CNB, core needle biopsy; DCIS, ductal carcinoma *in situ*; DCISM, ductal carcinoma *in situ* with microinvasion; IDC, invasive ductal carcinoma.

CNB nuclear grade, comedo necrosis, ERPgR status, and preoperative size (unpaired *t*-test) were not significantly related to invasion by CNBDCIS.

The logistic regression analysis (backward stepwise selection) showed that the following were significant predictive factors of invasion by CNBDCIS: palpable tumor (yes to no, OR 3.25), MMG category group (category 4 or 5 to categories 1, 2, or 3, OR 4.69) and MMG microcalcifications (no to yes, OR 0.24) (Table 2).

Analysis of the predictors of positive surgical margins for CNBDCIS. Thirty-six (27.5%) of the 131 CNBDCIS patients had positive margins after a postoperative pathological examination. The results of our univariate analysis (Fisher's exact test) of the clinicopathological factors of CNBDCIS related to positive surgical margins are presented in Table 3. Palpable tumor, MMG microcalcifications, MMG mass, and the operative procedure were significantly related to positive surgical margins for CNBDCIS. Patient age, MMG category group, tumor invasion, CNB nuclear grade, and preoperative size (unpaired *t*-test) were not significantly related to positive surgical margins for CNBDCIS.

The logistic regression analysis (backward stepwise selection) revealed that the operative procedure (conservative surgery to total mastectomy, OR 21.4) and MMG microcalcifications (yes to no, OR 3.35) were the significant factors related to positive surgical margins for CNBDCIS (Table 4A). The logistic regression analysis (backward stepwise selection) in conservative surgery revealed that MMG microcalcifications (yes to no, OR 3.23) was the only significant factor related to positive surgical margins for CNBDCIS (Table 4B). The rate of positive margins with MMG microcalcifications in conservative surgery was 50% (22/44), and that without MMG microcalcifications was 24% (13/55).

Table 2 Logistic regression analysis for CNBDCIS tumor invasion

Factor	Odds ratio	*p*-value
(Intercept)	0.244 (0.0951–0.625)	0.00329
Palpable tumor	3.250 (1.3200–7.970)	**0.0102**
MMG category group	4.690 (1.8300–12.000)	**0.00131**
MMG microcalcifications	0.239 (0.0923–0.620)	**0.00325**

Table 3 Clinicopathological factors related to positive margins

		Positive margin		
Factor	Group	No	Yes	*p*-value
n		95	36	
Palpable tumor (%)	No	31 (33.0)	22 (61.1)	0.005
	Yes	63 (67.0)	14 (38.9)	
MMG category group (%)	1, 2, 3	40 (42.1)	18 (50.0)	0.437
	4, 5	55 (57.9)	18 (50.0)	
MMG microcalcifications (%)	No	56 (58.9)	13 (36.1)	0.03
	Yes	39 (41.1)	23 (63.9)	
MMG mass (%)	No	41 (43.2)	24 (66.7)	0.019
	Yes	54 (56.8)	12 (33.3)	
US category group (%)	2, 3	25 (26.3)	13 (36.1)	0.287
	4, 5	70 (73.7)	23 (63.9)	
Operative procedure (%)	1. Partial mastectomy	61 (64.2)	26 (72.2)	
	2. Total mastectomy	31 (32.6)	1 (2.8)	
	3. Skin sparing mastectomy	1 (1.1)	4 (11.1)	
	4. Nipple sparing mastectomy	2 (2.1)	5 (13.9)	
Operative procedure group (%)	2	31 (32.6)	1 (2.8)	<0.001
	1, 3, 4	64 (67.4)	35 (97.2)	
Invasion (%)	DCIS	53 (55.8)	25 (69.4)	0.169
	DCISM (15)+IDC (38)	42 (44.2)	11 (30.6)	
CNB nuclear grade (%)	Low	55 (58.5)	15 (41.7)	0.141
	Intermediate	27 (28.7)	17 (47.2)	
	High	12 (12.8)	4 (11.1)	
Preoperative size	Mean (sd) cm	2.56 (1.63)	2.90 (1.89)	0.302

Table 4A Logistic regression analysis for positive margins

Factor	Odds ratio	*p*-value
(Intercept)	0.0142 (0.00171–0.118)	0.0000815
MMG microcalcifications	3.3500 (1.43000–7.820)	**0.00527**
Operative procedure group	21.4000 (2.72000–168.000)	**0.00358**

Table 4B Logistic regression analysis for positive margins in conservative surgery

Factor	Odds ratio	*p*-value
(Intercept)	0.31 (0.166–0.577)	0.00022
MMG microcalcifications	3.23 (1.370–7.620)	**0.00739**

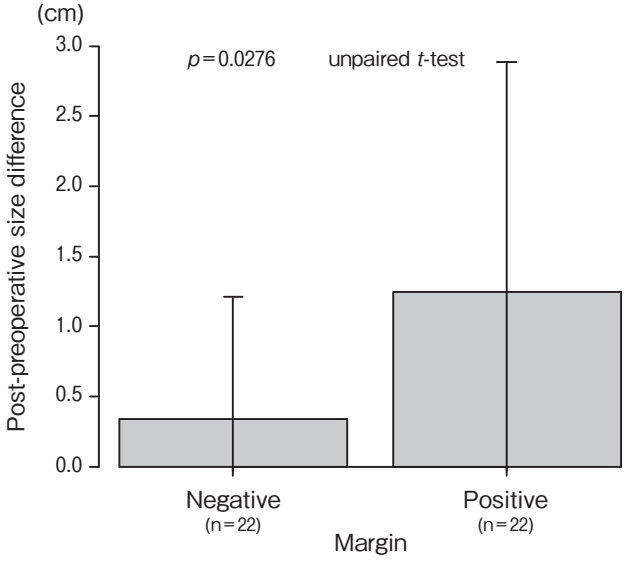

Fig. 1 Post − preoperative size differences (pathological definitive size − preoperative size) in conservative surgeries for patients with MMG microcalcifications.

In the 44 conservative surgeries of patients with MMG microcalcifications, the post- to pre-operative size difference (pathological definitive size-preoperative size) in the margin-positive group (1.24 cm) was significantly larger than that in the margin-negative group (0.34 cm) (Fig. 1).

Discussion

In a study using resected specimens, the incidence of CNBDCIS being upgraded to invasive cancer after pathological examination was 0% to 59% [3]. The clinical predictors of such upgrade are as follows: larger tumor [3,5,6], palpable mass [3,5], mass on mammography [3,4], Breast Imaging Reporting and Data System (BI-RADS) category 4 or 5 [3,5], biopsy device [3,5], nuclear grade at CNB [3,5,7,8], comedo necrosis at CNB [8,9], and overexpression of human epidermal growth factor 2 (HER2) [10].

In the present study, the logistic regression analysis demonstrated palpable mass (yes to no), MMG category (4 or 5 to 1,2 or 3) and MMG microcalcifications (no to yes) to be predictors of an upgrade. Although these findings concerning palpable mass and MMG category (similar to BI-RADS category) are consistent with previous reports, the other factors are not. First, the preoperative size of DCIS and that of the upgraded tumors were similar in our series. Nuclear grade and comedo necrosis at CNB were not related to upgrading, provided that comedo necrosis was not significant on meta- analysis. Among the above underestimation predictors, a large vacuum-assisted stereo-guided CNB can provide a more accurate diagnosis with a lower rate of underestimation. In our series, all CNB procedures were performed under US, and a vacuum-assisted biopsy (VAB) was used only for lesions with microcalcifications without a mass. As a result, the rate of underestimation by VAB was 11.1% (1/9). However, a case selection bias may have been present.

MMG microcalcifications were a negative predictor of upgraded CNBDCIS in the present study. The underestimation rate of CNBDCIS with MMG microcalcifications was 25.8% (16/62), and that without MMG microcalcifications was 53.6% (37/69). In a large series (506 cases of CNBDCIS) evaluated by Kim *et al.* [5], the underestimation rate of CNBDCIS with MMG microcalcifications (33.9%) was significantly lower than that without MMG microcalcifications (66.1%) by univariate analysis ($p<0.001$). Their report is consistent with ours. The meta-analysis also revealed that the mammographic mass (vs. calcification only) is significantly associated with upgraded invasion by CNBDCIS [3].

On the other hand, in the report by Miyake *et al.* [6] microcalcification was not a predictive factor of invasive cancer. Houssami *et al.* [7] found that the size of microcalcifications on imaging was significantly related to invasive breast cancer in women with newly diagnosed DCIS on vacuum-assisted CNB. Thus, MMG microcalcifications and the upgrading of CNBDCIS should be further investigated. It is notable that masses with

microcalcifications have a high upgrade rate (41%, 7/17). Wiratkapun *et al.* [8] reported that the upstaging rate of masses with calcification was as high as 66% (25/38).

Regarding positive surgical margins, although conservative breast surgery for DCIS is widely accepted as a surgical treatment [1,2,22], positive surgical margins are highly correlated with the local recurrence of breast cancer [11-13]. Hassan *et al.* [18] reported that among 249 patients, positive margins were identified in 104 (41.8%), with a positive rate of 25% in 125 mastectomies and 59% in 124 conservative surgeries. In the present study, 27.5% of the 131 patients and 35.3% of the 99 conservative surgeries had positive margins. Although only 9 of 31 mastectomies were examined using 5-mm serial sections in this study, the rate of positive margins in conservative surgery may be consistent with previous reports. Lesions that were ≥1.55 cm in size were reported to have a relative risk of positive margins. The clinicopathological factors related to positive margins were larger-sized DCIS on mammograms [15-17], the volume of the resected specimen [17], and high-grade [15] or low-grade DCIS [14]. Several studies of DCIS demonstrated that the margin-positive resection rates were 30-60% in conservative surgery [14-18].

Although radiation therapy after conservative surgery can control local recurrence in margin-positive patients [23-25], a margin-free surgical outcome is desired. Previous investigations found no relationship between MMG microcalcifications and positive margins. In one DCIS study, the rates of microcalcifications were 70-90% [14-16]. In the present study, DCIS and IDC of CNBDCIS were included, and the overall rate of MMG microcalcifications was 47.3%. In the conservative surgeries, the positive margin rate in the patients with MMG microcalcifications was 50%, and the corresponding rate in the patients without MMG microcalcifications was 24%.

Based on the results of the logistic regression analysis, MMG microcalcifications had the strongest relationship with positive margins. Moreover, although there was no significant difference in preoperative tumor size between our margin-positive and-negative groups, the post-preoperative size differences in the margin-positive group (1.24 cm) were significantly larger than those in the margin-negative group (0.34 cm) in conservative surgery for the patients with MMG microcalcifications. This phenomenon may be explained by the fact that small DCIS ducts without calcification are commonly seen at the edges of DCIS tumors with microcalcifications without a mass. Therefore, a larger stump should be taken in patients with MMG microcalcifications who undergo conservative surgery.

Dillon *et al.* [16] reported that mammographic underestimation of pathological size was closely related to positive margins. Unfortunately, in the present study we could not detect any preoperative factor of microcalcifications on MMG (distribution or shape or preoperative size) that was related to a positive margin. The only factor related to a positive margin was the post- vs. pre-operative size difference.

Axillary treatment is not necessary in cases of true DCIS. A routine SLNB is not required for the treatment of CNBDCIS after conservative surgery [26-28], and a secondary SLNB is only recommended when the postoperative pathological examination reveals invasive cancer. However, until now, we have preferred to perform an SLNB for most patients with CNBDCIS because of the relatively high underestimation rate of CNBDCIS and because the lymphatic drainage may have changed, resulting in an inaccurate SNLB. However, based on our present findings, for patients with CNBDCIS who have a low risk of tumor invasion (*i.e.*, those with non-palpable tumors; MMG category 1,2 or 3; or MMG microcalcifications without mass), we intend to perform a partial mastectomy with a sufficient stump—especially for patients with MMG microcalcifications without SLNB—in the future.

This study has some limitations. First, the number of patients was relatively small (n=131). Although our surgeons are qualified to read mammography findings by the Japan Central Organization on Quality Assurance of Breast Cancer Screening, a radiologist did not participate in this study. Thus, there may be some differences in the judgment of the MMG categories. Moreover, we did not separate MMG calcifications into categories based on the distribution or shape, to avoid complexity. We defined calcifications that were 0.5-3 mm in size produced in the tumor as MMG microcalcifications. HER2 status was not evaluated because the CNB specimens of only half of the patients were examined. HER2 should be examined in a future study.

Based on the logistic regression analysis results, the predictors of CNBDCIS being upgraded to invasive

cancer were a palpable mass (yes to no, OR 3.25), MMG category (4 or 5 to 1,2 or 3, OR 4.69), and MMG microcalcifications (no to yes OR 0.24). The predictors of positive surgical margins for CNBDCIS were the operative procedure (conservative surgery to total mastectomy, OR 21.4) and MMG microcalcifications (yes to no, OR 3.35). Therefore, MMG microcalcifications are a negative predictor of upgrading of CNBDCIS and a positive predictor of positive surgical margins for CNBDCIS.

Conservative surgery did not result in satisfactory outcomes for clear margins. We will improve the procedure based on the present data.

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